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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YOUNG, SHAWQUIA	

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,344	VERGNAULT ET AL.	
	Examiner	Art Unit	
	SHAWQUIA YOUNG	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 and 14-24 are currently pending in the instant application. The finality of the previous Office Action has been **withdrawn** because of an improper 103 reference used in the pending 103 rejections. Claims 1-12 and 14-24 are rejected in this Office Action.

I. *Response to Arguments*

Applicants' arguments, filed on July 21, 2009, have been fully considered and have been found persuasive relating to the use of the reference Schafer-Korting in the various 103 rejections. As discussed in the telephonic interview with Applicants' attorneys, the finality of the previous Office Action will be withdrawn and the Schafer-Korting reference will not be used in the 103 rejections because it is not considered prior art.

II. *Rejection(s)*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall

not be negatived by the manner in which the invention was made.

Claims 1-5, 8 and 14-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano (US 5,506,222) in view of Mueller, et al. in further view DrugBank (http://redpoll.pharmacy.ualberta.ca/drugbank) and of Mehnert,et al. and zur Mtihlen, et al.

Regarding claims 1 and 2, the instant Application is drawn to a formulation comprising spironolactone in an oriented crystalline lipid matrix for application to skin or mucosa. Stefano teaches spironolactone for topical application (column 11, claim 1) in a lipid matrix (column 12, claim 2, Substituted unsaturated fatty acids), but is silent regarding oriented crystalline nanoparticles. Mueller, et al. teaches solid lipid nanoparticles (50 to 1000 nm) for various applications such as topical (See page 162, section 2 and page 169, section 8) having a drug enriched core with a lipid crystal shell, formed as a function of the lipid's melting point and the relative solubilities of the drug and the lipid (See pages 164-167, section 3). The drug enriched core is formed when the drug precipitates before the lipid crystallizes. Because spironolactone (7a-acetylthio-3- oxo-17a-pregn-4-ene-21,17-carbolactone) is practically insoluble in water and has a Log P of 4.3 (See Drugbank entry for Spironolactone), the lipid nanoparticulate form of the drug forms such that the lipid crystal shell's hydrophilic "side" would face "outward," because the hydrophobic "side" would face "inward" toward the encapsulated lipophillic spironolactone. Mehnert, et al. (at Section 4.2 on page 179) further teaches that photon

correlation spectroscopy is the state of the art measurement technique for particle size determinations of particles in the range of "a few nanometers to about 3 microns."

Because of the distinct advantages of using solid lipid nanoparticles for topical application (i.e., their solid state of the particle matrix, the ability to protect chemically labile ingredients against chemical decomposition, possibility to modulate drug release, etc.) it would have been obvious to the person of ordinary skill in the art at the time the invention was made to have combined the formulation taught by Stefano with the liquid crystalline nanoparticulate lipid taught by Muller, et al obtain a topical dosage form of spironolactone with bioavailability resulting from the use of nanoparticulates.

Regarding claims 8, 14-19, 23 and 24, Muller, et al and Stefano are discussed above, with Stefano teaching the use of topical spironolactone compositions to treat the effects of increased androgenic activity including acne and hirsutism (abstract). These topical formulations comprise glyceryl monoesters, e.g. glyceryl monostearate (column 6, line 26), which are inherently crystalline under certain conditions of temperature, and other components of a cosmetically suitable cream base (column 4, lines 54 to 63) with additional excipients designed to promote drug delivery at the active site within the skin strata in order to obtain a therapeutic effect (column 5, Example 1 et seq.). Thus, it would have been obvious to the artisan of ordinary skill to combine the topical spironolactone formulation and dosing information of Stefano with the distinct advantages of using solid lipid nanoparticles for topical administration of Muller, et al. to treat the effects of increased androgenic activity (e.g., acne and hirsutism) in patients

with a need for such treatment using a topical preparation.

Regarding claim 20, combining the distinct advantages of using solid lipid nanoparticles for topical application of Muller, et al. with the "incorporated substance for use in topical treatment of acne" (e.g., spironolactone) as taught by Stefano would have been obvious to a person of ordinary skill in the art to obtain a topical dosage form with a bioavailable active ingredient resulting from the use of nanoparticulates rather than additional formulation components.

Regarding claims 1, 21 and 22, Muller, et al, Mehnert, et al., and Stefano are discussed above, but they do not teach specific particles in the size range of from 300 to 900 nanometers. The adjustment of particular conventional working conditions (e.g., determining result effective particle sizes beneficially taught by the cited references, especially within the broad ranges recited in claims), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the artisan of ordinary skill. Accordingly, this type of modification would have been well within the purview of the person of ordinary skill in the art and no more than an effort to optimize results. Also it was well established in In re Rose, 105 USPQ 237 (CCPA 1995), that selection of particle size is not a patentable modification in the absence of unobvious results.

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Muller, et al. in further view of Sjoblom (Emulsions-a fundamental and practical approach, pages 64-65, 1992, Kluwer Academic Publishers). Stefano and Muller, et al. are discussed above with Stefano further teaching glycerol monoesters (e.g., glyceryl monostearate, column 6, line 26), but they are silent regarding lipid crystallization temperature. Sjoblom teaches lipids with a crystallization temperature in the recited range such as 1-monopalmitin with a crystallization temperature of 75.9 (page 65, table 2), and further teaches beta-crystal of the monoglycerides (pages 64-65). Adjustment of crystallization temperature by judicious selection of formulation components such as these monoesters or monoglycerides yields an extent of crystallinity useful in topical formulations of nanoparticulate spironolactone formulation and would have been well within the purview of a person of ordinary skill in the art at the time the invention was made.

Claims 6, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Muller, et al. in further view of Hansen (US 6,228,383 B 1) and Klein, et al. (US 6,013,637). Regarding claims 6 and 7, Stefano and Muller, et al. are discussed above, but are silent regarding the solvent in which the nanoparticulate is formed. Hansen teaches that the lipid crystals are formed from polar liquids such as water and glycerol (column 6, lines 23 to 53), and that the lipid crystals are comprised of glyceryl monoesters of C1-8 fatty acids (Id.). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have combined the nanoparticulates taught by Stefano and Muller, et al. with the solvent and lipid

formulation components (specifically their inherent physical properties) taught by Hansen in order to obtain a product with the physical properties necessary to effect a solid state product at a temperature range suitable for typical topical cosmetic preparations.

Regarding claims 9-12, Hansen and Muller, et al. are discussed above with Hansen further teaching that the composition may be characterized as a suspension (column 14, line 46, thus in view of Muller, et al. a "nanosuspension") and that it further comprises a stabilizer (e.g., emulsifying agent, antioxidant, preservative, solubilizing agent, column 14, lines 52-67), which would have been an obvious addition to the formulation in order to maintain the suspension over the time and temperature ranges required to yield a useful product.

Hansen and Muller, et al. are both silent regarding sodium docusate as a stabilizer per se, but the person of ordinary skill in the art would recognize the term "stabilizer" as referring to any of a number of classes of compounds including surface active agents. Hansen teaches "solubilizing agents" (column 14, line 65), and as indicated in Klein, et al, sodium docusate is a stabilizing agent used in topical pharmaceuticals (See column 2, lines 29-33 and column 4, lines 29-35). Thus, the claimed stabilizer is equivalent to the teachings of Hansen in view of Klein, et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18, 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, while the specification is enabling for a method of treating acne, hirsutism, androgenic alopecia and rosacea does not provide enablement for a method of treating any condition that responds to anti-androgens. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention is a a method of treating acne, hirsutism, androgenic alopecia and rosacea.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art

would recognize that in regards to therapeutic effects of cognitive disorders by inhibiting ACE would make a difference.

Applicants' claims are drawn to a method for treating a condition that responds to anti-androgens. A method for treating a condition that responds to anti-androgens is a broad claim and thus encompasses treating conditions such as prostate cancer.

Applicants' claims are drawn to the treatment of prostate cancer. It is the state of the prior art that prostate cancer treatment often depends on the stage of the cancer. How fast the cancer grows and how different it is from surrounding tissue helps determine the stage. Treatment may include surgery, radiation therapy, chemotherapy or control of hormones that affect the cancer.
(URL:http://www.nlm.nih.gov/medlineplus/prostatecancer.html)

Hence, in the absence of a showing of correlation between all the diseases encompassed by the claims as capable of treatment by anti-androgens, such as prostate cancer one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the use of anti-androgens, for example, since treatment protocols for prostate cancer depend on the stage of the disease.

The amount of direction present and the presence or absence of working examples

The only direction or guidance present in the instant specification is minimal. There are no working examples present for the treatment of any condition that responds to anti-androgens such as prostate cancer.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is drawn to a method of a condition that responds to anti-androgens. Applicants' claims include conditions that are known and those that have yet been discovered.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all conditions such as prostate cancer would be benefited by the inhibition of androgens would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to

determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention in a method of treating a condition that responds to anti-androgens. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting these method claims.

IIII. *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/

Examiner, Art Unit 1626

/Rebecca L Anderson/

Primary Examiner, Art Unit 1626